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RESEARCH ARTICLE

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Demographic, hemodynamic characteristics, and therapeutic trends of pulmonary hypertension patients: The Pulmonary Hypertension Mexican registry (REMEHIP)

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Abstract

Data on demographic characteristics and therapeutic approaches in Latin American pulmonary arterial hypertension (PAH) patients are scarce. Pulmonary Hypertension Mexican registry (REMEHIP) is a multicenter Mexican registry of adult and pediatric patients, including prevalent and incident cases. Objective: assess clinical characteristics, treatment trends, and in-hospital outcomes. Inclusion: age >2 years, diagnosis of pulmonary hypertension (PH) (groups 1 and 4), right heart catheterization with mPAP ≥25 mmHg, PWP ≤ 15 mmHg, and PVR > 3 Wood unit (WU). We included 875 PH patients, 619 adults, 133 pediatric idiopathic PAH (IPAH), and 123 chronic thromboembolic pulmonary hypertension (CTEPH) patients.

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We enrolled 48.4% of the incident and 51.6% of the prevalent adult and pediatric patients. PAH adults: age 43 ± 15, females 81.9%, functional class (FC) (I/II) 66.5%, 6-min walk distance (6MWD) 378 ± 112 m, mPAP 57.3 ± 19.0 mmHg, confidence interval (CI) 3.3 ± 1.5 L/min/m^2, PVR 12.0 ± 8.1 WU. PAH pediatrics: age 9 ± 5, females 51.1%, FC (I/II) 85.5%, 6MWD 376 ± 103 m, mPAP 49.7 ± 13.4 mmHg, CI 2.6 ± 0.9 L/min/m^2, PVR 16.4 ± 13.5 WU. CTEPH: age 44 ± 17, females 56.1%, FC (I/II) 65.5%, 6MWD 369 ± 126 m, mPAP 49.7 ± 13.4 mmHg, CI 2.6 ± 0.9 L/min/m^2, PVR 10.5 + 6.5 WU. When we analyzed the IPAH group separately, it sustained a high functional class I/II incidence. REMEHIP shows better functional class in young females with severe PAH than in American and European patients. Also, PAH pediatric patients had a better functional class than other registries. However, our registry also shows that our population's access to specific pharmacologic treatments is still far from optimal.

KEYWORDS
chronic thromboembolic pulmonary hypertension, pulmonary arterial hypertension, pulmonary hypertension, registry

INTRODUCTION

Pulmonary hypertension (PH) is a worldwide vascular disease characterized by a progressive increase in pulmonary vascular resistance and pulmonary arterial pressure, secondary vascular and right ventricular (RV) remodeling, dysfunction, heart failure syndromes, and premature death. Significant medical advances have occurred in the last two decades, including more systematic assessment and the availability of new therapeutic approaches to improving life quality and survival.[1] Registries in developed countries enhanced our understanding of select aspects of pulmonary arterial hypertension (PAH), including new data on epidemiology, demography, clinical presentation, treatment, and prognosis.[2,3] Despite the evidence from developing countries,[4–10] data on clinical characteristics and current care strategies in Latin American PH patients are scarce.[5,7] High-quality criteria in clinical registries[11,12] are needed to understand if the knowledge from clinical trials was applied correctly. Also, if their results are reproducible in daily clinical practice. We reported the global findings in the Pulmonary Hypertension Mexican registry (REMEHIP) based on 875 well-characterized PH patients.

REGISTRY DESIGN

Previously, we published the REMEHIP (ClinicalTrials.gov:NCT02252705) protocol, including definitions.[1] In brief, REMEHIP is a multicenter registry collecting data on adult and pediatric, prevalent, and incident PH patients. The primary objective was to assess clinical characteristics, treatment trends, and in-hospital and 4-year outcomes. Inclusion criteria: patients aged >2 years with the diagnosis of PH (groups 1 and 4, World Health Organization) and right heart catheterization (RHC). We use the classification of PAH proposed by the European Society of Cardiology Guidelines 2015[13] since the registry starts in this period.[1] A mean pulmonary artery pressure ≥25 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and pulmonary vascular resistance >3 Wood units. We detected potential patients by echocardiography at nonspecialized centers and sent them to RHC confirmation and enrollment at the referral centers. Besides proven PH by RHC, for the etiologic diagnosis of PAH and chronic thromboembolic pulmonary hypertension (CTEPH), all patients underwent laboratory and pulmonary function tests, electrocardiography, echocardiography, V/Q scan, high-resolution computed tomography with contrast, or pulmonary angiography. Also, an acute vasodilator challenge was attempted in most idiopathic PAH (IPAH) patients.[14] In addition, we included prevalent (>3 months since diagnosis) and incident patients (diagnosis of PH 3 months before enrollment).[1] All the investigators had experience in the diagnosis and treatment of PH. We used current high-quality registry recommendations,[11,12] data collection, and analysis. Then, investigators sent the data to the registry-coordinating center via a website (http://www.remehip.mx/). The coordinating center

monitored electronic case report forms. Also, we randomly monitored data quality in 20% of centers. All participating sites had regular access to a data entry clerk, and the coordinating center provided technical support. Investigators at all sites underwent training using the electronic database, study definitions, and real-time access to professional advice from the coordinating center. We performed follow-ups by telephone and during office visits. An executive committee set out the policies for publication or presentation at national and international meetings. The institutional ethics and research committees approved the protocol in all participating centers, and all patients provided an informed consent form.

STATISTICAL ANALYSIS

This first descriptive report uses percentages, means, medians, and standard deviations.

RESULTS

We only analyzed demographics, hemodynamic characteristics, and therapeutic trends. We did not include any follow-up data. As shown in Table 1, we included 732 patients with PAH (18% pediatrics) and 123 patients with CTEPH. We enrolled 48.4% of the incident and 52.6% of the prevalent PH patients. The proportion of incident patients was 66.7%, and prevalent patients was 33.3% in CTEPH patients. The mean age was 43 ± 15 in PAH and 44 ± 17 in CTEPH patients. The female gender proportion was 81.% and 51.1%, respectively (Table 1). Both groups had a long interval from onset symptoms to RHC; a high proportion had functional class I–II and 6-min walk distance (6MWD) > 360 m (Table 1). B-type natriuretic peptide and N-Terminal Pro B-type natriuretic peptide were determined in 41.2% of patients (Table 1). Echocardiography showed severe pulmonary systolic pressure, RV dilatation, and normal TAPSE. Table 1 also shows the hemodynamics of PAH and CTEPH patients. Both groups had severe PH. However, PAH patients had numerically higher cardiac output and index than CTEPH patients. More frequently, pericardial effusion was present in PAH (10%) and CTEPH (15%). Diuretics and vitamin K antagonist oral anticoagulants drove PAH-supportive treatment in both groups; however, anticoagulant therapy was numerically higher in CTEPH. The PAH-specific treatment included phosphodiesterase-5 inhibitors (PDE5-i) and endothelin receptor antagonists (ERAs) in CTEPH, and these drugs were more frequently used in PAH (Table 1).

The main etiologic groups in the 619 adult PAH patients included the following: familiar or idiopathic (40.2%), congenital heart disease (CHD) (40.2%), and associated collagen tissue disease (CTD) (18%). Other PAH etiologies (anorexigenic-induced, porto-pulmonary, and human immunodeficiency virus [HIV]) were infrequent (0.5%). Table 2 shows basal demographics and functional class of IPAH (including familiar PAH), CHD- and CTD-associated PAH patients. CHD patients were younger, and females were less predominant in this group than IPAH and CTD patients. Also, CHD had a higher proportion of patients in functional classes I and II. IPAH and CHD had better 6MWD than CTD patients (Table 2). In those with CHD-associated PAH, the most frequent shunts were atrial (48%) and ventricular septal defect (22%), patent ductus arteriosus (15%), and combined defects (15%). We did not include in the analysis anorexigenic-induced ($n = 3$, median age 58 years, 67% females, 50% in functional class II), porto-pulmonary ($n = 3$, median age 44 years, 33% female, 66% in functional class II), and HIV ($n = 3$, median age 41 years, 66% female, 66% in functional class III), given its low numbers of patients. Table 3 shows PAH patients' demographic, clinical, and hemodynamic characteristics in some registries from developed and developing countries. We identified differences in age, gender, functional class, and cardiac index with the patients in the REMEHIP registry. We did not perform any tests to compare.

Table 4 shows the demographic, echocardiographic, hemodynamics, and basal therapeutic characteristics of 133 pediatric patients. The age at diagnosis was 9 ± 5 years, with a similar gender distribution. Although shorter than adult patients, we identified a long interval from the onset of symptoms to RHC (19 ± 25 months). At enrollment, a high proportion had functional class I (32.3%) and II (53.2%). B-type natriuretic peptide was determined in 21.8% of pediatric patients (Table 4). Table 4 also shows 6MWD, echocardiography, hemodynamic findings, and therapeutic trends in this group. Diuretics drove supportive treatment, and oral anticoagulants were less frequent than in adult PAH. Analyzed separately (Table 5), pediatric patients had CHD-associated (70%), IPAH (27%), and porto-pulmonary and CTD-associated (1% each). The most common CHD were combined defects at 50%, ventricular septal defects at 22%, atrial septal defects at 16%, and patent ductus arteriosus at 12%. Table 6 shows only some demographic, clinical, and hemodynamic variables from randomly selected registries and REMEHIP's findings in pediatric patients. We did not perform any tests to compare variables. An essential finding was a better functional class.

TABLE 1 Demographic, functional, echocardiographic, and hemodynamic characteristics and treatment of 742 patients with pulmonary hypertension in REMEHIP registry.

Variable	PAH adults 619 patients (no, %)	CTEPH 123 patients (no, %)
Age, years (mean ± SD)	43 ± 15	44 ± 17
Gender, female	507/81.9	69/56.1
The time interval from onset symptoms to diagnosis, months (mean ± SD)	29 ± 47	24 ± 40
The time interval from onset symptoms to diagnosis, months, median (quartiles)	12 (6–36)	12 (6–24)
PAH etiologies		
Idiophatic or familiar	249/40.2	-
Congenital heart disease	249/40.2	-
Collagen tissue disease	111/18	-
Functional class at diagnosis	**No = 592**	**No = 116**
Functional class I	64/10.8	13/11.2
Functional class II	330/55.7	63/54.3
Functional class III	186/31.4	36/31.0
Functional class IV	12/2.0	4/3.4
6-min-walk distance, mean ± SD	378 ± 112	369 ± 126
B-type natriuretic peptide, median interquartile	**No = 180**	**No = 37**
B-type natriuretic peptide (ng/L)	92.4 (35.0–269.0)	66.0 (30.6−182.5)
N-Terminal Pro B-type natriuretic peptide, median interquartile	**No = 126**	-
N-Terminal Pro B-type natriuretic peptide (ng/L)	257.4 (45.8–1099)	-
Echocardiography (mean ± SD)	**No = 619**	**No = 123**
Pericardial effusion	60/10.0	18/15.0
TAPSE, mm	18.1 ± 4.9	17.3 ± 5.1
RVEDD/LVEDD		
1:1	47/54.0	7/63.6
2:1	33/37.9	2/18.2
>2:1	7/8.0	2/18.2
Hemodynamics (mean ± SD)		
Mean pulmonary artery pressure (mmHg)	57.3 ± 19.0	49.7 ± 13.4
Pulmonary wedge pressure (mmHg)	9.3 ± 3.7	9.5 ± 3.7
Right atrial pressure (mmHg)	8.0 ± 4.9	10.1 ± 5.8
Cardiac index (L/min/m^2)	3.3 ± 1.5	2.6 ± 0.9
Cardiac output (L/min)	5.3 ± 2.2	4.7 ± 1.4
Pulmonary vascular resistance (WU)	12.0 ± 8.1	10.5 + 6.5
Systemic vascular resistance (WU)	17.2 ± 7.6	17.8 ± 7.5
Supportive treatment		
Diuretics	307/49.6	67/54.5
Acenocoumarin	113/18.3	54/43.9

TABLE 1 (Continued)

Supportive treatment		
Warfarin	57/9.2	23/18.7
FXa inhibitors	33/5.3	14/11.4
Digoxin	113/18.3	20/16.3
Immunosuppressors	11/1.8	-
Calcium channel blockers	73/11.8	4/3.3
Phosphodiesterase-5 inhibitors	419/67.7	61/49.6
Endothelin receptor antagonists	204/33.0	19/15.4
Prostanoids	56/9.1	5/4.1
Soluble guanylate cyclase stimulator	20/3.2	9/7.3
Double therapy	181/29.2	19/15.5
Triple therapy	27/4.4	1/0.8

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; REMEHIP, Pulmonary Hypertension Mexican registry; RVEDD/LVEDD, right ventricular end-diastolic diameter/left ventricular end-diastolic diameter ratio; WU, Wood units.

TABLE 2 Demographic basal characteristics of adult patients with idiopathic, associated with congenital heart disease, and associated connective tissue disease PAH.

Variable	248 Idiopathic PAH patients[a] (no, %)	250 with congenital heart disease-associated-PAH patients (no, %)	112 with connective tissue disease-associated patients (no, %)
Age, years, mean ± SD	43.7 ± 15	39 ± 14	49 ± 13.5
Gender, women	207/85.2	189/76	99/88.4
FC at diagnosis (WHO)	**No = 236**	**No = 240**	**No = 106**
FC I	26/11	32/13.3	5/4.6
FC II	127/53.8	145/60.4	54/50.0
FC III	77/32.6	61/25.4	45/41.7
FC IV	6/2.5	2/0.8	4/3.7
6-min-walk distance, m (mean ± SD)	381 ± 114	384 ± 106	349 ± 116

Abbreviations: FC, functional class; PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus; WHO, World Health Organization.
[a]We did not include in this analysis, familial ($n = 8$), HIV ($n = 3$), porto-pulmonary ($n = 3$), and anorexigen drugs PAH patients.

DISCUSSION

The REMEHIP is the largest registry, including adult and pediatric PH patients in Latin America.[5–7] The relevant descriptive findings are as follows: First, as in other registries, IPAH-, CHD-associated PAH, and CTD-associated PAH were the most prevalent etiologic subgroups in PAH. Second, we identified a higher proportion of young female patients with a better functional class and cardiac hemodynamics than observed in other adult registries[2,3,5,9,15–18] and pediatrics IPAH patients.[19–23] Third, the high incidence of CHD-associated PAH in pediatric and adult patients underlying the necessity to implement strategies for early diagnosis of this potentially reversible PAH type.[24] Fourth, in contrast to current registries, specific treatment is driven by monotherapy (PD5-I) in IPAH adults and combination treatment (ERAs and PDE5-I) in the pediatric population. Finally, many CTPEH patients were under "off-label" specific treatment (Table 1).

Evidence-based medicine guides therapeutic decisions; the best evidence comes from randomized

TABLE 3 Demographic, clinical, and hemodynamic characteristics of PAH patients in some registries from developed and developing countries.

Variables	French (no = 674 pts, %)	UK (no = 482 pts, %)	REVEAL (no = 2525 pts, %)	Spanish (no = 866 pts, %)	Chinese (no = 276 pts, %)	Brazilian (no = 178 pts, %)	REMEHIP (no = 619 pts, %)
Age PAH (years)	50 ± 15	N/A	53 ± 14	45 ± 17	N/A	46 ± 15	42.6 ± 15
Patients with IPAH[a]	39.2	100	46.2	36.2	173 o 62.6	28.7	40
IPAH[a] (years)	52 ± 15	50 ± 17	53 ± 14	46 ± 18	33.4 ± 15.3	39.8 ± 14.8	43.7 ± 15
Female	65.3	69.9	79.5	71	69.9	77	85
FC I–II	25	15.8	44.3	31	48	54.5	65
FC III–IV	75	84.2	55.6	69	52	45.5	35
6MWD (m)	329 ± 109	292 ± 123	366 ± 126	363 ± 120	394 ± 114.2	383 ± 152	381 ± 114
Cardiac Index, (L/min/m^2)	2.5 ± 0.8	2.1 ± 0.7	2.4 ± 0.8	2.6 ± 0.9	2.5 ± 0.9	2.6 ± 0.8	3.05 ± 1.17
RAP (mmHg)	8 ± 5	10 ± 6	9.3 ± 5.6	9 ± 5	12.3 ± 6.4	10 ± 5	8.9 ± 5.02
PVRi (WU)	20.5 ± 10.2	13 ± 6	21.1 ± 12.5	12 ± 6	17.1 ± 6.4	10.4 ± 6.1	11.5 ± 7.72

Abbreviations: 6MWD, 6-min walk distance; FC, functional class; PAH, pulmonary arterial hypertension; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; REVEAL, registry to evaluate early and long-term PAH disease management; UK, United Kingdom; WU, Wood units.

[a]Includes familial PAH patients ($n = 8$).

controlled trials. However, the patients in these trials do not represent the real world, and higher-risk patients are not adequately represented.[12] Registries provide additional information from real-life clinical practice.[1,11,12] The Mexican registry REMEHIP, including incident and prevalent PH cases,[1] showed age differences, lower drug use,[25] and better functional class in adult and pediatric patients than other registries[2,3,5,9,15–18] (Tables 3 and 6). The high proportion of patients in functional classes I and II (>65%) remained (Table 1) even when we analyzed (Tables 2 and 5) idiopathic and CHD-associated PAH separately. We also observed the same trend in CTEPH patients (Table 1). This clinical presentation reproduced previous evidence from clinical trials[4,26] and registries[2,6,27] in IPAH and CTEPH Mexican patients. The reason for these findings in the Mexican population is uncertain. Given the cardiac index and 6MWT found in our registry, misclassification of the functional class is unlikely. We speculated that the adaptative remodeling process might involve unique mechanisms, probably at the molecular level, working together to maintain an RV adaptive state.[28,29] It is also possible that the "better adaptation" may be driven by their younger age and the higher frequency of CHD as the primary mechanism. More research on experimental and clinical models is necessary to understand the RV performance in Mexican patients only.

The REMEHIP registry demonstrated a high proportion of young female patients among IPAH, CHD-, and CTD-associated patients. The hormonal theory about PAH's pathogenesis triggers, specifically estrogens inducing cellular proliferation, was highly possible in female IPAH patients.[2] This incidence is similar to Brazilian, Spanish, and American registries and differs from European patients (Table 3). In support of this is that the female proportion is less prominent in the pediatric PAH population, as shown by other pediatric registries (Table 5). Age is also lower in REMEHIP, Chinese, and Brazilian registries than in European registries. The reason for these demographic differences is unclear.

Another characteristic of the Mexican PH phenotype was a higher incidence of CHD- associated (adult 40% and pediatric 71%) compared with the registry to evaluate early and long-term PAH disease management (19.5%) [2] and non-Hispanic Whites (5%), African-Americans (1%), and the Hispanic population (10%) living in the United States.[30] The published incidence of CHD-associated is also lower in Brazil (7.8%),[5] Spain (16%),[17] and France (11.2%) registries. Likely explanations for the high prevalence of CHD-associated PAH in our country include the lack of access to health systems, living in distant regions, or late referral to tertiary centers.[24] Early detection of PH in CHDs and access to treatment are still challenges in most Latin American countries.[24] One pending task for the health systems would be to identify this population in an early reversible stage to avoid the transition into irreversible complex vascular lesions.[31] Based on a high incidence of endovascular and surgery

TABLE 4 Demographic, functional, echocardiographic, and hemodynamic characteristics and treatment of 133 PAH pediatric patients in REMEHIP registry.

Variable	PAH pediatrics 133 patients (no, %)
Age, years, mean ± SD	9 ± 5
Gender, female	68/51.1
The time interval from onset symptoms to diagnosis, months, mean ± SD	19 ± 25
The time interval from onset symptoms to diagnosis, months, median (quartiles)	10 (4-23)
Functional class at diagnosis (WHO)	**No = 124 patients**
Functional class I	40/32.3
Functional class II	66/53.2
Functional class III	14/11.3
Functional class IV	4/3.2
B-type natriuretic peptide, median interquartile	**No = 29 patients**
B-type natriuretic peptide, ng/L	66.1 (41.5–216.1
6-min-walk distance, mean ± SD	376 ± 103
Echocardiography (mean ± SD)	**No = 133**
Pulmonary artery systolic pressure (mmHg)	71.9 ± 28.1
Right ventricular diastolic diameter (mm)	25.3 ± 13.1
Pericardial effusion	-
TAPSE (mm)	16.7 ± 4.6
RVEDD/LVEDD	
1:1	22/66.7
2:1	10/30.3
>2:1	1/3.0
Hemodynamics (mean ± SD)	
Mean pulmonary artery pressure (mmHg)	53.0 ± 19.2
Pulmonary wedge pressure (mmHg)	10.6 ± 3.1
Right atrial pressure (mmHg)	8.8 ± 3.7
Cardiac index (L/min/m^2)	3.9 ± 2.6
Cardiac output (L/min)	3.5 ± 1.9
Pulmonary vascular resistance (WU)	16.4 ± 13.5
Systemic vascular resistance (WU)	20.6 ± 12.2
Supportive treatment	
Diuretics	89/66.9
Acenocoumarin	19/14.3
Warfarin	2/1.5
FXa inhibitors	-
Digoxin	6/4.5
Immunosuppressors	-
Calcium channel blockers	5/3.8

(Continues)

TABLE 4 (Continued)

Echocardiography (mean ± SD)	No = 133
Phosphodiesterase-5 inhibitors	78/58.6
Endothelin receptor antagonists	77/57.9
Prostanoids	1/0.75
Soluble guanylate cyclase stimulator	-
Double therapy	43/32.3
Triple therapy	-

Abbreviations: REMEHIP, Pulmonary Hypertension Mexican registry; RVEDD/LVEDD, right ventricular end-diastolic diameter/left ventricular end-diastolic diameter ratio; WHO, World Health Organization; WU, Wood units.

TABLE 5 Demographic basal characteristics of 133 idiopathic and associated congenital and connective tissue disease PAH pediatric patients.

Variable	Idiopathic, 38 patients (no, %)	Congenital heart disease-associated, 94 patients (no, %)	Connective tissue disease-associated, one patient (no, %)
Age, years, mean ± SD	9 ± 5	9 ± 5	12
Gender, women	42/44.7	26/68.4	-
FC at diagnosis (WHO)	**No = 33**	**No = 91**	
FC I	7/21.2	33/36.3	-
FC II	19/57.6	47/51.6	-
FC III	4/12.1	9/10.0	1/100
FC IV	3/9.1	2/2.2	-
6-min-walk distance, m (mean ± SD)	394 ± 94	365 ± 107	435

Abbreviations: FC, functional class; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

advances,[32] governmental measures and national health system programs are needed to prevent PAH, reducing the economic impact on health care systems.[24]

Currently, standard and specific treatments are the foundation of PAH patients' care. Although supportive therapy is available worldwide, the characteristics and therapeutic trends are poorly described.[2,5,33] Despite a higher incidence of functional classes I and II, we observed a high proportion of diuretic use in all PH groups (Tables 1 and 4). Whether diuretics use reduces clinical worsening or compensates for lack of access to combined specific treatment is an unanswered question.[34] Digoxin had a similar trend, especially in CHD-PAH patients, and its use is possibly indicated and limited to decreasing ventricular rate in atrial fibrillation and flutter patients. We do not have strong evidence of digoxin's efficacy in PAH.[14] Despite these limitations, both drugs are used as nonspecific but available standard treatment in the Mexican population. Despite European guidelines and recommendations,[14] oral anticoagulation use was 74% in CTEPH patients (Table 1). Oral anticoagulation was 34% in the IPAH group. European guidelines recommend individual decision-making since oral anticoagulation increases bleeding risk without robust data in IPAH patients.[14]

The specific PAH treatment has evolved progressively and increased in complexity and evidence for efficacy. Currently, we have 14 Food and Drug Administration-approved active drugs[35] and four administration routes, alone or in combination, to improve exercise capacity and quality of life, delaying disease progression. In addition, the activin and growth factor inhibitors may be approved.[36] Current recommendations based on risk stratification include initial combination therapy.[14] However, broad access to specific treatment is still challenging in most Latin American countries. Most adult and pediatric PAH patients received monotherapy with PD5-i; a lower proportion of ERAs were in

TABLE 6 Demographic, clinical, and hemodynamic characteristics of some registries from developed and developing countries in pediatric patients.

Variables	TOPP, 317 pts (%)	French, 50 pts (%)	REVEAL, 216 pts (%)	UK, 216 pts (%)	IPAH, children 77 pts (%)	REMEHIP, 133 pts (%)
Age PAH (years)	7[a]	5.1 ± 4.8[a]	15	N/D	N/D	9 ± 5
IPAH (years)	7[a]	N/D	15	7.37	7 ± 4	9 ± 5
Patients with IPAH	57.0	60.0	56.5	27.8	77	28.6
Female	59.0	48.0	64.0	45.8	65	51.1
FC I–II	63	71	52	N/D	25	85.5
FC III–IV	37	28	49	N/D	75	14.5
6MWD (m)	417	421 ± 65	435 ± 124	N/D	N/D	376 ± 103
Cardiac index, (L/min/m^2)	3.7	3.8 ± 1.8	3.7 ± 1.7	2.7 ± 1.03	3.1 ± 1.1	3.9 ± 2.6
RAP (mmHg)	7	N/D	7 ± 4	7.69 ± 3.7	5 ± 3	8.8 ± 3.7
PVR (WU)	16	20 ± 19	17 ± 15	22.01 ± 10.9	22 ± 13	20.6 ± 12.1

Abbreviations: 6MWD, 6-min walk distance; FC, functional class; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; REMEHIP, Pulmonary Hypertension Mexican registry; REVEAL, registry to evaluate early and long-term PAH disease management; WU, Wood units.

[a]Age at diagnosis.

REMEHIP patients. Also, a low percentage received combined treatment based on PD5-i and ERAs. Therefore, access to double or triple combination treatment, up-front or sequential, is limited in our country. In addition, despite current therapeutic recommendations, a higher proportion of CTEPH patients receive "off-label" monotherapy treatment with PD5-i or ERAs (Table 1). Therefore, this finding underlines the urgent need to increase effective regional thromboendarterectomy and pulmonary balloon angioplasty programs to consolidate a network and national reference center. By achieving these targets, we can improve CTEPH patient care in Mexico.

Cardiovascular registries are essential sources of real-world evidence informing clinical practice and health policy.[37] Despite their inherent limitations, registry data influence clinical practice and treatment guidelines.[37] In addition, REMEHIP fills this critical knowledge gap in the Mexican population. Recently, the 2018 World Symposium on Pulmonary Hypertension proposed a risk-based approach to therapy founded mainly on the independent validation of risk assessment strategies from European and US PAH registries.[37] High-quality PAH registries will have enormous potential regarding large, well-characterized patients worldwide, linking health administrative data or biobanks.[37] In addition, large-scale international registries could help us better understand PAH health resource utilization in the real world, geographic and sociocultural gaps in diagnosis and treatment, and the link between pharmacogenomic differences in populations and long-term outcomes.[37] Other opportunities include the potential to integrate validated patient-reported data from mobile devices and digital health data or physical activity tracking apps with PAH registries.[37]

REMEHIP's limitations include not being a population-based epidemiological study, so we cannot exclude bias related to select centers. We had to use the definition proposed by the European Society of Cardiology in 2015[13] because of the time the protocol was performed and published.[1] Perhaps the most important limitation is the limited monitoring visits. (20%) to data accuracy. Another limitation was no community hospital inclusion. In addition, considering the uncontrolled capture data, interpreting the therapeutic approach is limited. It was not possible to identify the functional class in all patients. Finally, several PAH subtypes (porto-pulmonary, drug, and HIV) are poorly represented.

CONCLUSIONS

Data from REMEHIP, a Mexican registry, shows better functional class in young females with severe PAH than American and European patients. In addition, limited access to specific treatment characterizes the Mexican

PAH phenotype in adult patients. Also, PAH pediatric and CTEPH patients had a better functional class than other registries. Nevertheless, national programs for early CHD detection, regional networks, a national reference center for CTEPH, and access to optimal pharmacologic treatment are still necessary to improve Mexican PH patient care.

AUTHOR CONTRIBUTIONS

Carlos Jerjes-Sanchez wrote the protocol, designed the case report form, analyzed the results, and wrote and reviewed the final manuscript. Alicia Ramírez-Rivera participated in the protocol design, analyzed the results, and wrote and reviewed the final manuscript. Nayeli Zayas Hernandez and Guillermo Cueto Robledo were a top enroller and reviewed the final manuscript. Humberto Garcia-Aguilar, Pedro Gutiérrez-Fajardo, Mario Seoane García de León, Francisco Moreno Hoyos-Abril, Miguel Ernesto Beltrán Gámez, and Jose Elizalde participated in the protocol design, analyzed the results, and reviewed the final manuscript. Julio Sandoval protocol designed, results analysis, and wrote and reviewed the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Research Ethics Committees and Research Committees approved the research protocol and gave informed consent to each participating center.

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